Tuberculosis, Diabetes, Serum Drug levels

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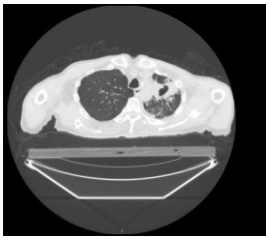
No disclosures

Case

- 72 yo male DM, ESRD on hemodialysis MWF, former farmer, embalmer, and pipe smoker, cavitary upper lobe lesion (PET CT)
- Bronch 3+ AFB positive
- Treatment regimen?



Case

- 1.5 months
- Doing OK
- Sensitivities "low level" INH resistant in MGIT
- Serum drug levels for Rifampin
- Rifampin level 1.98 ug/ml (8-24)
- What would you do?

Case

- Rif 900qd, Moxi 400qd, PZA and EMB 3x week after HD
- 2.5 months
- Doing OK
- Still 3+ smear positive
- Cultures still positive
- What would you do?

Case

- Rif 900qd, Moxi 400qd, PZA and EMB 3x week after HD
- 2.5 months
- Doing OK
- Still 3+ smear positive
- Cultures still positive
- What would you do?
- Re-send DST: same susceptibilities
- Re-send drug levels: RIF 16, Mox 2, PZA 18, Emb 3

Overview

Diabetes increases the risk of progression to active TB disease
(odds **2.4-8.3** compared to non-diabetics)
and likely higher for poorly controlled diabetics

Diabetes/TB prevalence will increase globally

When a diabetic has TB, treatment outcomes are worse (compared to non-diabetics w TB)

Drug concentrations are suboptimal for most DM/TB patients

The New England
Journal of Medicine

VOLUME 210 JANUARY 4, 1934 NUMBER 1

THE ASSOCIATION OF DIABETES AND TUBERCULOSIS*

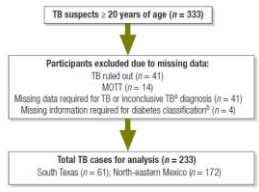
Epidemiology, Pathology, Treatment and Prognosis

BY HOWARD F. ROOT, M.D.†

(a) The development of pulmonary tuberculosis in juvenile diabetics occurred more than ten times as frequently as among non-diabetic Massachusetts grade and high school children.

(b) Pulmonary tuberculosis developed in 8 per cent of diabetic patients within three years of recovery from coma.

Attributable risk of TB from Diabetes > HIV in Texas/Mexico border



Age (years)	Diabetes			HIV infection		
	RR (95% CI)	$AR_{exposed}$ (%)[a]	$AR_{population}$ (%)[b]	RR (95% CI)	$AR_{exposed}$ (%)[a]	$AR_{population}$ (%)[b]
South Texas						
20+ (n=61)	2.7 (1.6–4.4)	63	26	17.8 (6.5–9.0)	94	5
20–34 (n=20)	0.9 (0.1–6.8)	–9	1	34.4 (8.0–147.7)	97	6
35–64 (n=32)	5.1 (2.6–10.2)	80	48	12.2 (2.9–50.9)	92	5
65+ (n=9)	1.7 (0.5–5.8)	41	22	0[c]	NA	NA
NE Mexico						
20+ (n=172)	3.1 (2.3–4.2)	68	24	16.0 (7.5–34.0)	94	3

Restrepo et al. *Bull WHO* 2011

Diabetes is the leading identified risk factor for TB in Virginia (10-15%)

http://www.vdh.virginia.gov/TB/documents/2013_annual_final.pdf

Table 5. Tuberculosis Cases by Selected Risk Factors: Virginia, 2009-2013

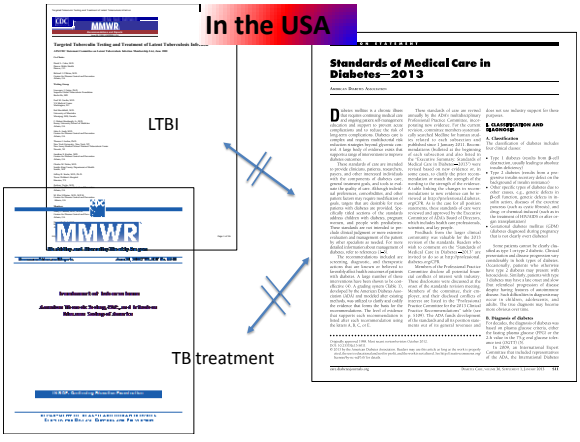
	2009		2010		2011		2012		2013	
Total Cases	**273**		**268**		**221**		**235**		**180**	
	No.	%	No.	%	No.	%	No.	%	No.	%
Occupation										
Health Care	11	4.0	12	4.5	7	3.2	8	3.4	5	2.8
Migrant	0	0.0	0	0.0	0	0.0	1	0.4	0	0.0
Corrections	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Type of Residence										
Long Term Care	3	1.1	8	3.0	5	2.3	2	0.9	4	2.2
Prison/Jail	4	1.5	8	3.0	8	3.6	6	2.6	0	0.0
Homeless	9	3.3	12	4.5	1	0.5	10	4.3	8	4.4
Co-Morbidity										
Diabetes	37	13.6	37	13.8	31	14.0	27	11.5	26	14.4
HIV	18	6.6	8	3.0	9	4.1	12	5.1	10	5.6
Substance Use										
Alcohol	21	7.7	23	8.6	17	7.7	21	8.9	13	7.2
IDU	6	2.2	1	0.4	0	0.0	2	0.9	2	1.1
Non-IDU	6	2.2	4	1.5	13	5.9	15	6.4	7	3.9

Screening for diabetes in new TB patients can be highly effective (India)

	Number of TB patients whose DM status was ascertained [a]	Number with previously known DM [b]	Number of DM newly diagnosed [c]	Additional Yield [c/(b+c)*100]	Number needed to screen (NNS) [(a−b)/c]
Type of TB					
New Smear Positive Pulmonary TB	307	87	70	45%	3.1
New Smear Negative Pulmonary TB	37	4	7	64%	4.7
New Extra-pulmonary TB	128	15	21	58%	5.3
Relapse	35	12	8	40%	3.3
Treatment after Failure	19	7	2	22%	6.0
Treatment after Default	26	3	7	70%	3.3

Overall, number of **TB patients needed to screen** (with HbA1c) in order **to detect one new case of diabetes was just 4**.

Balakrishnan et al. *PLoS ONE* 2012



Overview

Diabetes increases the risk of progression to active TB disease
(odds **2.4-8.3** compared to non-diabetics)
and likely higher for poorly controlled diabetics

Diabetes/TB prevalence will increase globally

When a diabetic has TB, treatment outcomes are worse (compared to non-diabetics w TB)

Drug concentrations are suboptimal for most DM/TB patients

No special presentation

No difference in location of disease or lung cavitation

	Year	Study location	Participants (n)		Lower lung more commonly involved?	More cavitary lesions?	More diffuse involvement?
			With diabetes	Without diabetes			
Weaver[45]	1974	USA	20	182	Yes	--	--
Marais[37]	1980	South Africa	9	427	Yes	--	--
Ikezoe et al[44]	1992	Japan	31†	71	No	Yes	Yes
Morris et al[26]	1992	Texas, USA	20	20	No	No	No
Umut et al[46]	1994	Turkey	37	37	No	Yes	Yes
Kuaban et al[47]	1996	Cameroon	--	273‡	Yes	--	--
al-Wabel et al[24]	1997	Saudi Arabia	28	38	No	--	--
Bacakoglu et al[48]	2001	Turkey	92	92	No§	No§	No
Perez-Guzman et al[49,50]	2000–01	Mexico	192	130	Yes	Yes	Yes
Shaikh et al[51]	2003	Saudi Arabia	187	505	Yes	--	--
Wang et al[52]	2005	Taiwan	99	362	No	Yes	--
Wang et al[54]	2008	Taiwan	74	143	Yes	Yes	--
Al-Tawfiq et al[53]	2009	Saudi Arabia	57	78	--	No	--

Dooley et al. *Lancet ID* 2009

Diabetics in Indonesia more likely to be culture-positive at 6 months of treatment (22%)

Table 3. Treatment response and outcome of patients with tuberculosis (TB) with and without diabetes mellitus (DM).

Period, variable	No. (%) of patients with TB			
	With DM (*n* = 94)	Without DM (*n* = 540)	Crude OR (95% CI)	Adjusted OR (95% CI)
Intensive phase				
AFB negative[a]	67 (71.3)	455 (84.3)	...	...
AFB positive	17 (18.1)	54 (10.0)	2.14 (1.17–3.9)	1.90 (0.82–4.42)
No sputum sample available, hospital transfer, and/or study default	8 (8.5)	31 (5.7)	...	...
Death	2 (2.1)	0 (0)	...	...
Culture result positive for *Mycobacterium tuberculosis*	7/41 (17.1)	68/372 (18.3)	0.92 (0.39–2.16)	0.90 (0.30–2.68)
End of treatment				
AFB negative[a]	70 (74.5)	435 (80.6)	...	...
AFB positive	4 (4.3)	17 (3.1)	1.46 (0.48–4.47)	1.06 (0.17–6.60)
No sputum sample available, hospital transfer, and or study default	18 (19.1)	88 (16.3)	...	...
Death	2 (2.1)	0 (0)	...	...
Culture result positive for *M. tuberculosis*[b]	6/27 (22.2)	32/333 (9.6)	2.69 (1.01–7.14)	7.65 (1.89–30.95)

NOTE. The intensive phase was the first 2 months of treatment, and end of treatment was at 6 months. AFB, acid-fast bacilli.

- **14.8% prevalence of undiagnosed DM in new TB patients**

Alisjahbana et al. *Clin Infect Dis* 2007

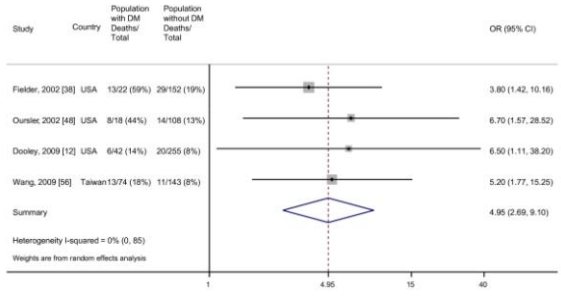
- In Maryland, **odds of death were 6.5 times higher** (p=0.039) for diabetics than non-diabetics with TB, even adjusting for HIV, age, weight, and foreign birth

½ of deaths were not TB related

- Time to sputum culture conversion was longer (49 days for diabetics vs 39 days for non-diabetics, p=0.09)

Dooley et al. *Am J Trop Med Hyg* 2009

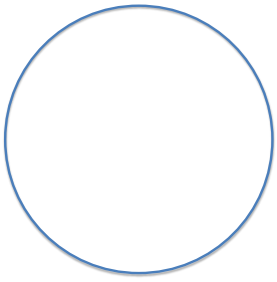
All cause mortality increased in diabetics during TB treatment



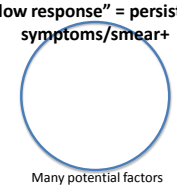
Baker et al. *BMC Med* 2011

Outcomes during treatment for Tb

Most do well (>90%)

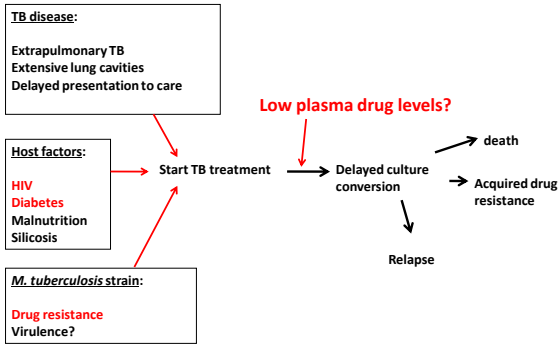


Some don't
Death < delayed cx conversion < "slow response" = persistent symptoms/smear+



Many potential factors
Extensive disease
Drug resistance
HIV
Other comorbidities/smoking
Low drug levels
Diabetes
.....

Worse outcomes.....What can we do about it?



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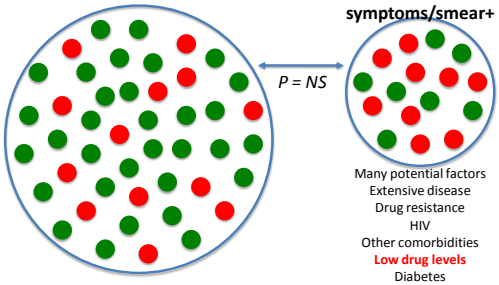
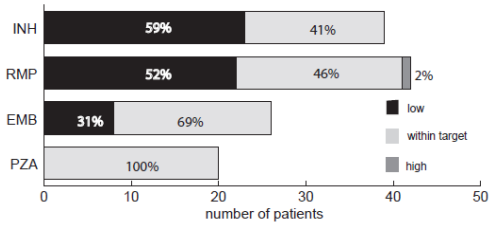


Many potential factors
Extensive disease
Drug resistance
HIV
Other comorbidities
Low drug levels
Diabetes
.....

- We have been routinely checking serum anti-TB drug concentrations in "slow responders" since ~2007 (thanks to some add'l funding)
  - ~14% of all Tb patients, defined as no improvement in sx or persistent smear +
- Diabetics were **6.3 times more likely to be slow responders** (p<0.001) adjusted for age, gender, foreign birth, prior TB episodes, cavitary disease, HIV, alcohol and tobacco use.
  - ~40% of diabetics
- Among slow responders, **diabetics had significantly lower serum rifampin levels** (estimated peak C_{2h})

Heysell et al. *Emerg Infect Dis* 2010

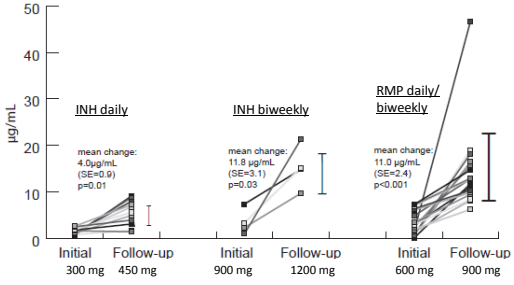
Majority of slow responders had low C_{2hr} levels of INH and rifampin



82% had low levels to one of INH or RMP, hard to predict which one

Heysell et al, *Emerg Infect Dis*, 2010

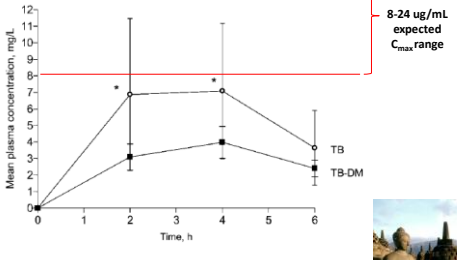
Drug levels usually correct after first dose adjustment



I spans C_{2hr} expected range

Heysell et al, *Emerg Infect Dis* 2010

Low rifampin levels is not new
Rifampin exposure significantly reduced in diabetics from Indonesia



Nijland et al. *Clin Infect Dis* 2006

Low drug levels matter, at least in vitro

TABLE 2. TB drug activity (TDA) values and $C_{2\ h}$ drug levels at 14 days of TB treatment for Tanzanian patients[a]

Drug	Mean drug $C_{2\ h}$ ± SD (μg/ml)		*P* value
	TDA ≤ 2.0 (n = 9)	TDA > 2.0 (n = 7)	
Isoniazid	1.31 ± 1.2	2.56 ± 1.2	0.05
Rifampin	0.77 ± 1.3	4.65 ± 3.2	0.005
Ethambutol	0.83 ± 0.37	1.68 ± 0.93	0.03
Pyrazinamide	20.3 ± 7.3	28.0 ± 10.7	0.11

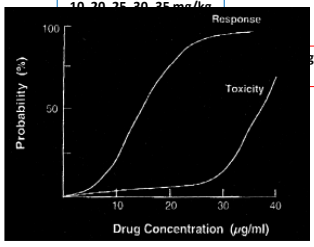
Heysell et al. *Antimicrob Agents Chemother* 2011

What is the right* dose of rifampin?

*In 1971 the dose of **10 mg/kg** was arbitrarily chosen without a maximum tolerated dose study.

N= 68, smear positive PTB randomized to RIF 10, 20, 25, 30, 35 mg/kg

·Drop in culture
·Mean C_{max} 10 m
group



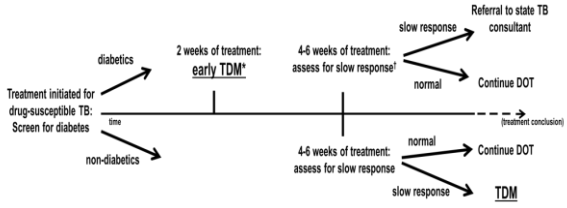
Boeree et al. CROI 2013

It would not surprise me if eventually we use 900mg RIF routinely, or in high risk pts…….

In 2011, an initiative was started to measure isoniazid and rifampin levels (these 2 drugs only, PZA usually fine, EMB usually dropped) in all diabetics at 2 weeks of TB therapy (instead of waiting for ~40% to be slow responders)

The Virginia Algorithm

http://www.vdh.state.va.us/epidemiology/diseaseprevention/programs/tuberculosis/documents/TDMRecommendationsandProceduresRrevised082013Final.pdf



Instead of only self-report and prior DM diagnoses, we now recommend checking HbA1C on all
>6.5: education/resource packet, referral
<6.5: education/resource packet

In TB Diabetes, if these early levels are low…

Table 2. Dose adjustment for diabetics with early routine TDM

	Normal drug levels	Sub-target INH, normal RIF	Normal INH, Sub-target RIF	Sub-target INH and Sub-target RIF
Initiation regimen*	Continue INH 300 mg M-F; RIF 600 mg M-F	Finish initiation with INH 450 mg M-F; RIF 600 mg M-F	Finish initiation with INH 300 mg M-F; RIF 900 mg M-F	Finish initiation with INH 450 mg M-F; RIF 900 mg M-F
Continuation regimen	Continue INH and RIF (biweekly acceptable)	INH 900 mg and RIF 600 mg, thrice weekly	INH 900 mg and RIF 900 mg, thrice weekly	INH 900 mg and RIF 900 mg, thrice weekly

- Single incremental increases without rechecking
  - Easy, practical, generally increases the levels, patients are doing well at this point so we don't go for broke

Early TDM in diabetics corrected low drug concentrations in the majority and may limit slow response

As expected many had low levels

•Of the 21 diabetics, **16 (76%) had a C_{2hr} value below the expected range for isoniazid** (mean 2.1±1.5 μg/ml; expected 3-5), **rifampin** (mean 6.6 ±4.3 μg/ml; expected 8-24) **or both**

Levels generally correct with single incremental increase

•15 patients had follow-up concentrations after dose adjustment, all increased and 12 to the expected range (including all for rifampin).
•In practice, what our algorithm does is shunt most diabetics to at least 3x weekly therapy during continuation phase, with INH 900/RIF 900, while keeping to a 6 month total duration

Patients do well, better than expected norms for TB

•**88% of diabetics** with early TDM and pulmonary TB had **sputum culture conversion <2 mos**.

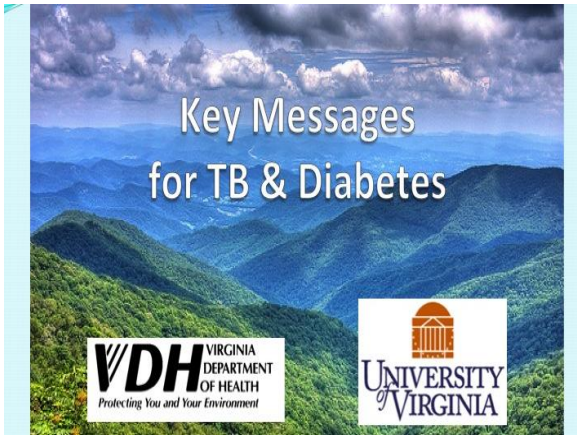
May limit the need for prolonged treatment and program resources

•**total statewide burden of slow response decreased** from 1.6 patients/mo (40% diabetic) to 1.2 patients/mo (12.5% diabetic)

Heysell et al. NTCA 2013

Acknowledgments

- UVA
  - Scott Heysell, Tania Thomas, Suzanne Stroup
- VDH
  - Jane Moore, Suzanne Keller, Debbie Staley, Denise Dodge
- Virginia TB Foundation



About this Resource

TB outreach workers (ORWs) and nurses have an opportunity to promote education and key messages to people over an extended time, during directly observed therapy (DOT). This resource was developed to support ORWs and nurses as they provide education to individuals and community groups. It addresses TB and diabetes. People diagnosed with TB should be checked for diabetes because having diabetes can affect the treatment and management of TB.

Educating Patients

This flip chart is designed to:

- Complement and reinforce TB education given at the time of TB diagnosis,
- Promote adherence to and completion of TB

Conducting the TB and Diabetes Education Sessions

- Since TB and diabetes can cause great concern or worry, frame educational information in positive rather than negative terms whenever possible.
- Give specific feedback and be realistic in your advice. For example, if it is unlikely that a patient will totally stop smoking and/or drinking, suggest that the patient reduce use of cigarettes and alcohol.
- If you do not know the answer to a question, tell the patient that you do not know but that you will talk to the TB case manager and bring the answer back for the patient.
- Do not overload a patient with information; use clear, simple language and avoid medical terminology.
- Be aware that there may be a stigma about TB and some people believe that the disease is inherited. Explain that TB is spread through

Using this Flip Chart

- The flip chart uses patient centered questions, which requires the health care worker to listen, respond and tailor information to the patient's needs. This process should promote the development of the patient/health care worker relationship.
- Education topics are organized according to the standard TB and diabetes management plans. This supports patient monitoring and promotes adherence to TB and diabetes control activities.
- Prompts for the health care worker are provided on the back of each page of the flip chart to guide discussion. The content has been designed to support patient monitoring related to TB and diabetes care and reinforce positive health behaviors.
- When using the flipchart, hold the picture straight so people can see it clearly.
- Show the picture and ask "what do you see in this picture?" to encourage discussion.
- Allow time for the patient to answer, then summarize the good points and add any

It is important to involve people in discussing the pictures in the flip chart because:

- People remember only 20% of what they hear
- They remember 50% of what they hear and see
- They remember 90% of what they practice and do

This flip chart was adapted from the Australian Respiratory Council's flip chart, "Key Messages for TB & Diabetes."

Week 1

Help stop the spread of TB

How can you help stop the spread of TB?